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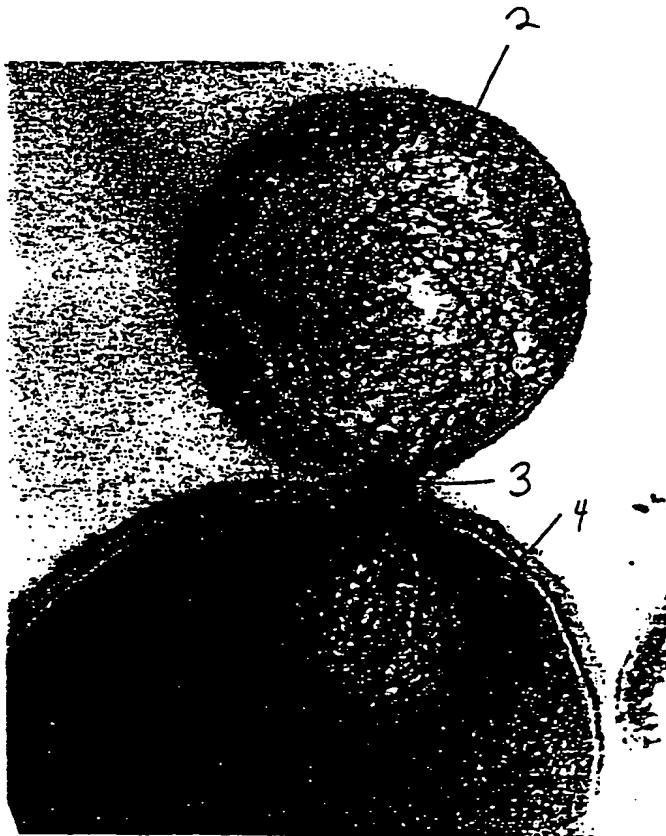
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(81) Designated States (national): AE, AG, AL, AM, AT, AU,
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NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
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(54) Title: THE PARENTERAL USE OF BACTERIAL PHAGE ASSOCIATED LYSING ENZYMES FOR THE THERAPEUTIC
TREATMENT OF BACTERIAL INFECTIONS



(57) Abstract: The present invention discloses a method and composition for the treatment of bacterial infections by the parenteral introduction of a therapeutic agent comprising an effective amount of at least one lytic enzyme produced by a bacteria infected with a bacteriophage specific for said bacteria wherein the lytic enzyme is selected from the group consisting of lytic enzymes, and modified lytic enzymes such as shuffled lytic enzymes, chimeric lytic enzymes, and combinations thereof, wherein said lytic enzyme is in an appropriate carrier for delivering the lytic enzyme into a patient. The therapeutic agent may additionally include a holin enzyme, which may be a shuffled holin enzyme or a chimeric holin enzyme. The injection can be done intramuscularly, subcutaneously, or intravenously.



patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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- *without international search report and to be republished upon receipt of that report*

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(71) Applicant (for all designated States except US): NEW HORIZONS DIAGNOSTICS, CORPORATION [US/US]; 9110 Red Branch Road, Columbia, MD 21045-2014 (US).

(72) Inventors: and

(73) Inventors/Applicants (for US only): FISCHETTI, Vincent [US/US]; 448 Joan Court, West Hempstead, NY 11552 (US). LOOMIS, Lawrence [US/US]; 11374 Buckeberry Path, Columbia, MD 21044 (US).

(74) Agent: BENT, Stephen, A.; Foley & Larder, 3000 K Street, N.W., Suite 500, Washington, DC 20007-5109 (US).

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WO 01/51073 A3

(54) Title: THE PARENTERAL USE OF BACTERIAL PHAGE ASSOCIATED LYSING ENZYMES FOR THE THERAPEUTIC TREATMENT OF BACTERIAL INFECTIONS

(57) Abstract: The present invention discloses a method and composition for the treatment of bacterial infections by the parenteral introduction of a therapeutic agent comprising an effective amount of at least one lytic enzyme produced by a bacteria infected with a bacteriophage specific for said bacteria wherein the lytic enzyme is selected from the group consisting of lytic enzymes, and modified lytic enzymes such as shuffled lytic enzymes, chimeric lytic enzymes, and combinations thereof, wherein said lytic enzyme is in an appropriate carrier for delivering the lytic enzyme into a patient. The therapeutic agent may additionally include a holin enzyme, which may be a shuffled holin enzyme or a chimeric holin enzyme. The injection can be done intramuscularly, subcutaneously, or intravenously.

What we claim is:

- 1) A method for the treatment of bacterial infections, comprising:
administering parenterally an effective amount of a therapeutic agent, said therapeutic agent comprising at least one enzyme produced by a bacteria infected with a bacteriophage specific for said bacteria, wherein said at least one enzyme is selected from the group consisting of lytic enzymes, modified lytic enzymes, and combinations thereof; and
a carrier for delivering said lytic enzyme to the site of the infection.
- 2) The method according to claim 1, wherein said modified lytic enzymes are selected from the group consisting of chimeric lytic enzymes, shuffled lytic enzymes, and combinations thereof.
- 3) The method according to claim 1, further comprising at least one holin enzyme.
- 4) The method according to claim 3, wherein said at least one holin enzyme is a shuffled enzyme.
- 5) The method according to claim 3, wherein said at least one holin enzyme is a chimeric enzyme.
- 6) The method according to claim 1, wherein the at least one enzyme is for the treatment of *Pseudomonas*.

- 7) The method according to claim 1, wherein the at least one enzyme is for the treatment of *Streptococcus*
- 8) The method according to claim 1, wherein the at least one enzyme is for the treatment of *Staphylococcus* .
- 9) The method according to claim 1, wherein the at least one enzyme is for the treatment of *Clostridium*.
- 10) The method according to claim 1, wherein said composition further comprises a buffer that maintains pH of the composition at a range between about 4.0 and about 9.0.
- 11) The method according to claim 10, wherein the buffer maintains the pH of the composition at the range between about 5.5 and about 7.5.
- 12) The method according to claim 10, wherein said buffer comprises a reducing reagent.
- 13) The method according to claim 12, wherein said reducing reagent is dithiothreitol.
- 14) The method according to claim 10, wherein said buffer comprises a metal chelating reagent.
- 15) The method according to claim 14, wherein said metal chelating reagent is ethylenediaminetetraacetic disodium salt.

- 16) The method according to claim 10, wherein said buffer is a citrate-phosphate buffer.
- 17) The method according to claim 1, further comprising a bactericidal or bacteriostatic agent as a preservative.
- 18) The method according to claim 1, wherein said at least one lytic enzyme is lyophilized.
- 19) The method according to claim 1, further comprising administering a concentration of about 100 to about 500,000 active enzyme units per milliliter of fluid in the wet environment of the nasal or oral passages.
- 20) The method according to claim 19, further comprising administering the concentration of about 100 to about 10,000 active enzyme units per milliliter of fluid in the wet environment of the nasal or oral passages.
- 21) The method according to claim 1, wherein said therapeutic agent is administered intravenously.
- 22) The method according to claim 1, wherein said therapeutic agent is administered intramuscularly.
- 23) The method according to claim 1, wherein said therapeutic agent is administered subcutaneously.
- 24) The method according to claim 1, wherein the therapeutic agent further comprises at least one complementary agent which potentiates the

bactericidal activity of the lysine enzyme, said complementary agent being selected from the group consisting of penicillin, synthetic penicillins bacitracin, methicillin, cephalosporin, polymyxin, cefaclor. Cefadroxil, cefamandole nafate, cefazolin, cefixime, cefmetazole, cefoniod, cefoperazone, ceforanide, cefotanme, cefotaxime, cefotetan, cefoxitin, cefpodoxime proxetil, ceftazidime, ceftrizoxime, ceftriaxone, cefriaxone moxalactam, cefuroxime, cephalexin, cephalosporin C, cephalosporin C sodium salt, cephalothin, cephalothin sodium salt, cephapirin, cephadrine, cefuroximeaxetil, dihydratecephalothin, moxalactam, loracarbef. mafate and chelating agents in an amount effective to synergistically enhance the therapeutic effect of the lysin enzyme.

- 25) The method according to claim 1, wherein said carrier comprises of distilled water, a saline solution, albumin, a serum, and any combinations thereof.
- 26) The method according to claim 1, wherein said carrier further comprises preservatives.
- 27) The method according to claim 26, wherein said preservatives comprise p-hydroxybenzoates.
- 28) The method according to claim 1, wherein said carrier comprises an isotonic solution for an injection, said isotonic solution comprising a compound selected from group consisting of sodium chloride, dextrose, mannitol, sorbitol, lactose, phosphate buffered saline, gelatin, albumin, a vasoconstriction agent and combination.

- 29) The method according to claim 28, wherein said further carrier further comprises DMSO.
- 30) The method according to claim 1, wherein said method is for the prophylactic treatment of infections.
- 31) The method according to claim 1, wherein said method is for the therapeutic treatment of infections.
- 32) The method according to claim 1, further comprising at least one enzyme which is not selected from the group consisting of at least one shuffled lytic enzyme, at least one chimeric lytic enzyme, and at least one holin lytic enzyme.
- 33) A composition for the treatment of bacterial infections, comprising:
 - a therapeutic agent comprising an effective amount of at least one enzyme produced by a bacteria infected with a bacteriophage specific for said bacteria and a carrier for the parental delivery of said lytic enzyme to the site of the infection, wherein said at least one enzyme is selected from the group consisting of lytic enzymes, shuffled lytic enzymes, chimeric lytic enzymes, and combinations thereof; and
 - a carrier for parenterally delivering said lytic enzyme to the site of the infection.
- 34) The composition according to claim 33, further comprising at least one holin enzyme.

- 35) The composition according to claim 34, wherein said at least one holin enzyme is a chimeric enzyme.
- 36) The composition according to claim 34, wherein said at least one holin enzyme is a shuffled enzyme.
- 37) The composition according to claim 33, wherein the at least one enzyme is for the treatment of *Pseudomonas*.
- 38) The composition according to claim 33, wherein the at least one enzyme is for the treatment of *Streptococcus*.
- 39) The composition according to claim 33, wherein the at least one enzyme is for the treatment of *Staphylococcus*.
- 40) The composition according to claim 33, wherein the at least one enzyme is for the treatment of *Clostridium*.
- 41) The composition according to claim 33, wherein said composition further comprises a buffer that maintains pH of the composition at a range between about 4.0 and about 9.0.
- 42) The composition according to claim 41, wherein the buffer maintains the pH of the composition at the range between about 5.5 and about 7.5.
- 43) The composition according to claim 41, wherein said buffer comprises a reducing reagent.

- 44) The composition according to claim 43, wherein said reducing reagent is dithiothreitol.
- 45) The composition according to claim 41, wherein said buffer comprises a metal chelating reagent.
- 46) The composition according to claim 45, wherein said metal chelating reagent is ethylenediaminetetraacetic disodium salt.
- 47) The composition according to claim 41, wherein said buffer is a citrate-phosphate buffer.
- 48) The composition according to claim 33, further comprising a bactericidal or bacteriostatic agent as a preservative.
- 49) The composition according to claim 33, wherein said at least one enzyme is lyophilized.
- 50) The composition according to claim 33, further comprising a concentration of about 100 to about 500,000 active enzyme units per milliliter of fluid in the wet environment of the nasal or oral passages.
- 51) The composition according to claim 50, further comprising the concentration of about 1000 to about 100,000 active enzyme units per milliliter of fluid in the wet environment of the nasal or oral passages.
- 52) The composition according to claim 33, wherein said therapeutic agent is administered intravenously.

- 53) The composition according to claim 33, wherein said therapeutic agent is administered intramuscularly.
- 54) The method according to claim 34, wherein said therapeutic agent is administered subcutaneously.
- 55) The composition according to claim 33, wherein the therapeutic agent further comprises at least one complementary agent which potentiates the bactericidal activity of the enzyme, said complementary agent being selected from the group consisting of penicillin, synthetic penicillins bacitracin, methicillin, cephalosporin, polymyxin, cefaclor. Cefadroxil, cefamandole nafate, cefazolin, cefixime, cefmetazole, cefoniod, cefoperazone, ceforanide, cefotanme, cefotaxime, cefotetan, cefoxitin, cefpodoxime proxetil, ceftazidime, ceftrizoxime, ceftriaxone, cefriaxone moxalactam, cefuroxime, cephalexin, cephalosporin C, cephalosporin C sodium salt, cephalothin, cephalothin sodium salt, cephapirin, cephadrine, cefuroximeaxetil, dihydratecephalothin, moxalactam, loracarbef. mafate and chelating agents in an amount effective to synergistically enhance the therapeutic effect of the lysin enzyme.
- 56) The composition according to claim 33, wherein said carrier comprises of distilled water, a saline solution, albumin, a serum, and any combinations thereof.
- 57) The composition according to claim 33, wherein said carrier further comprises preservatives.

- 58) The composition according to claim 57, wherein said preservatives comprise p-hydroxybenzoates.
- 59) The composition according to claim 33, wherein said carrier comprises an isotonic solution for an injection, said isotonic solution comprising a compound selected from group consisting of sodium chloride, dextrose, mannitol, sorbitol, lactose, phosphate buffered saline, gelatin, albumin, a vasoconstriction agent and combinations.
- 60) The composition according to claim 33, wherein said carrier further comprises DMSO.
- 61) The method according to claim 33, wherein said therapeutic agent is for the therapeutic treatment of infections.
- 62) The method according to claim 33, wherein said therapeutic agent is for the prophylactic treatment of infections.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 32876/119	FOR FURTHER ACTION <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. PCT/US 01/00913	International filing date (day/month/year) 12/01/2001	(Earliest) Priority Date (day/month/year) 14/01/2000
Applicant NEW HORIZONS DIAGNOSTICS, CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. **Certain claims were found unsearchable (See Box I).**

3. **Unity of invention is lacking (see Box II).**

4. With regard to the **title**,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EP 0 510 907 A (AGRICULTURAL & FOOD RES) 28 October 1992 (1992-10-28)</p> <p>page 2, line 1 -page 3, line 5 page 3, line 4 - line 6; claim 1 ---</p> <p style="text-align: right;">-/--</p>	<p>1,6, 8-20, 25-27, 30,31, 33,37, 39-51, 56-58, 60-62</p>

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *E* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

28 June 2001

12/07/2001

Name and mailing address of the ISA

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 02351 A (CIBA GEIGY AG ;UNIV CAMBRIDGE TECH (GB); LUZIO JOHN PAUL (GB); BRY) 23 January 1997 (1997-01-23) page 1, paragraph 1; claims 1,22 page 2, paragraph 1 page 5, paragraph 3 page 7, paragraph 2 ---	1,10-23, 25-31, 33, 41-54, 56-62
X	WO 96 07329 A (UNIV MARYLAND) 14 March 1996 (1996-03-14) page 1, line 2 - line 8; claims 1,19,20,55 page 7, line 28 -page 8, line 6 page 10, line 29 -page 11, line 7 ---	1,10-20, 25-27, 33, 41-51, 56-58, 61,62
X,P	US 6 056 954 A (FISCHETTI VINCENT A ET AL) 2 May 2000 (2000-05-02) cited in the application column 1, line 13 - line 16; claims 1-9 column 2, line 35 - line 41 column 3, line 5 - line 34 column 3, line 47 - line 60 ---	1,6,8, 10-23, 25-31, 33,37, 39, 41-54, 56-62
X,P	US 6 056 955 A (FISCHETTI VINCENT ET AL) 2 May 2000 (2000-05-02) cited in the application column 1, line 6 - line 9; claims 1,16,22 column 3, line 41 -column 4, line 9 ---	1,8, 10-23, 25-31, 33,39, 41-54, 56-62
A	WO 99 04809 A (AMBI INC) 4 February 1999 (1999-02-04) page 1, line 11 - line 27; claims 1,19 page 4, line 2 -page 5, line 1 page 5, line 29 - line 32 ---	1-62
		-/-

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; BABENKO IU S ET AL: "Enzymatic lysis of staphylococci in relation to their species and strain properties!. Fermentativnyi lizis stafilokokkov v zavisimosti ot ikh vidovykh i shtamovykh osobennostei." retrieved from STN Database accession no. 90297672 XP002170795 abstract & ANTIBIOTIKI I KHMiotERAPIIA, (1990 MAR) 35 (3) 20-2. ,</p> <p>-----</p>	1,8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/00913

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0510907	A 28-10-1992	GB 2255561 A AU 650737 B AU 1502392 A CA 2066387 A US 6083684 A US 5763251 A		11-11-1992 30-06-1994 22-10-1992 21-10-1992 04-07-2000 09-06-1998
WO 9702351	A 23-01-1997	AU 718184 B AU 6311696 A CA 2226258 A CN 1191572 A CZ 9704213 A EP 0842284 A HU 9900323 A JP 11509728 T NO 980021 A SK 1398 A		06-04-2000 05-02-1997 23-01-1997 26-08-1998 15-04-1998 20-05-1998 28-05-1999 31-08-1999 02-03-1998 16-05-2000
WO 9607329	A 14-03-1996	CA 2199478 A EP 0776163 A		14-03-1996 04-06-1997
US 6056954	A 02-05-2000	US 5997862 A WO 0119385 A US 6238661 B US 6017528 A US 5985271 A		07-12-1999 22-03-2001 29-05-2001 25-01-2000 16-11-1999
US 6056955	A 02-05-2000	WO 0119391 A		22-03-2001
WO 9904809	A 04-02-1999	AU 8509598 A BR 9811535 A CN 1269727 T EP 1001804 A HU 0002662 A NO 20000314 A PL 338178 A US 6028051 A ZA 9806593 A		16-02-1999 29-08-2000 11-10-2000 24-05-2000 28-12-2000 16-03-2000 09-10-2000 22-02-2000 04-02-1999